(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 225 189 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **07.10.92** (51) Int. Cl.5: **A61K 9/48**, A61K 47/00

(21) Application number: **86309305.0**

(22) Date of filing: **28.11.86**

(54) **Targeted enteral delivery system.**

(30) Priority: **29.11.85 IL 77186**

(43) Date of publication of application:
10.06.87 Bulletin 87/24

(45) Publication of the grant of the patent:
07.10.92 Bulletin 92/41

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 40 590
EP-A- 0 036 145
EP-A- 0 036 534
EP-A- 0 108 295
GB-A- 1 159 236

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EP 0 225 189 B1

Description

This invention relates to a targeted enteral delivery system which enables a medicament to be released at a region of the intestine such as the colon at which the medicament is not significantly adversely affected by digestive juices.

Certain drugs such as insulin and other proteins or peptides if administered orally to a patient and allowed to pass unprotected through the stomach, exhibit poor efficacy.

For example, the poor efficacy of orally administered insulin in diabetic patients is mainly due to two properties of this substance:

(a) insulin is a pancreatic hormone peptide and thus subject to proteolytic inactivation during the passage through the gastro-intestinal tract, mainly in its upper region;

(b) insulin has a high tendency for self-association to form high molecular weight oligomers and as a result of this increase in molecular weight the amount of insulin passing through enteral membranes by diffusion is not sufficient to achieve appreciable therapeutic effects.

It has been shown by coinventors of the present invention (Touitou et al., J. Pharm. Pharmacol. (1980), 32, 108-110) that significant hypoglycaemia can be induced in rats when insulin is injected intrajejunally in the presence of a non-ionic surfactant, Cetamacrogol™ $_{1000}$, as absorption promoter. They suggested that insulin absorption might be accomplished by oral administration of a suitably designed product containing insulin and surfactant provided that the insulin were protected against degradation by a suitable coating during its passage to the jejunal absorption site.

US-4406896 and US-4464363 describe rectally administered drug forms which include, in addition to the drug, an absorption promoter such as 5-methoxysalicylic acid for enhancing absorption of the drug into the bloodstream from the rectum.

Such rectal administration is, however, inconvenient to the patient.

GB-B-2123695 describes orally administrable dosage forms consisting of a tablet or capsule containing 5-amino-salicylic acid for local treatment of colonic or rectal disorders. The dosage form is coated with a 60 to 150 micron thick layer of Eudragit S - a commercially available anionic polymer which is a partly methyl esterified methacrylic acid polymer ("Eudragit" is a trade mark). The coating is insoluble in the gastric and intestinal juices below pH 7 but soluble in colonic juices, so that the oral dosage form remains intact until it reaches the colon.

EP-A-0036145 and EP-A-0036534 describe the use of hydroxyaryl or hydroxyaralkyl acids, salts, amides or esters for enhancing the rate of oral absorption of polar bioactive agents and β-lactams respectively, and mention the use of hydroxymethylpropylcellulose phthalate as an enteric coating. EP-A-0108295 describes the use of various long chain alcohols, fatty acids and glycerides as absorption promoters for β-lactams and mentions various enteric coatings including those of the individual acrylic copolymers Eudragit S & L. GB-A-1155236 also mentions the use of Eudragit S as an enteric coating.

US-A-4432966 describes compressed tablets for disintegration in the colon, which tablets contain active ingredients such as neomycin and prednisolone. The tablets are provided with a double coating, the inner of which contains microcrystalline cellulose and a film-forming polymer which is not degraded by a neutral or alkaline medium, and the outer of which is a pharmaceutically acceptable enteric coating.

However, such compositions have not been designed to allow significant amounts of active ingredient to be absorbed into the bloodstream.

Thus, although highly desirable from a practical point of view, unit dosage forms for the oral administration of drugs such as insulin, which drugs are susceptible to attack by the digestive juices, have not, to date, been successful.

The problem therefore is both to protect drugs such as peptides from proteolysis and to achieve useful absorption from the colon into the bloodstream. We have found a delivery system of a coated capsule with certain substances in the capsule contents which leads to an enhancement of absorption from the intestine.

This delivery system results in a decrease in drug inactivation and an increase in drug absorption.

The invention provides a capsule for oral administration of a pharmaceutically active ingredient (hereinafter "drug") which capsule is coated with a film of a film forming composition and containing a pharmaceutical composition, which composition comprises the drug, an absorption promoter capable of enhancing absorption of the drug from the intestine into the bloodsteam, and, if appropriate, a suitable pharmaceutically acceptable excipient. The film forming compositon comprises an acrylic polymer which is a mixture of acrylic copolymers such that the film is sufficiently insoluble at a pH below 7 as to be capable of protecting the capsule shell and pharmaceutical composition therein from the digestive juices until the capsule reaches a region in which the active ingredient will not be significantly adversely affected by the digestive juices, whereupon the film and capsule are capable of eroding or dissolving to allow release of the

drug into a region below th upper part of the small intestine for absoption therefrom into the bloodstream.

A targeted delivery syst m in accordance with the invention is especially applicable to any drug which (i) is poorly absorbed, and/or (ii) is degraded by the gastric or small-intestinal juices, and/or (iii) induces side effects in the stomach/small intestine, but is particularly useful for administration of therapeutically useful peptide or protein drugs, for example insulin, gastrin, pentagastrin, calcitonin, human growth hormone, glucagon, adrenocorticotrophic hormone, leutinising releasing hormone, enkephalin, oxycotin, parathyroid hormone, thyrotropic releasing hormone and vasopressin.

The capsules are adapted to effectively release the drug at any region within the lower part of the gastro-intestinal tract, where proteolysis is rather low. Such release may occur at any region below the upper part of the small intestine, including the lower part of the small intestine, and including the rectum. However, preferred capsules release the drug in the jejunum or colon, especially the colon.

A particularly preferred dosage form is one comprising insulin contained in gelatin capsules coated with a suitable polymer, such as a polyacrylic polymer which has pH dependent properties.

The capsule may be a soft or hard gelatin capsule.

A soft gelatin capsule shell is preferably prepared from a capsule composition comprising gelatin, or a substituted gelatin, e.g. phthallated or succinated gelatin, and a plasticiser such as a polyhydric alcohol, e.g. glycerol. For specific cases, a blend of polyhydric alcohols, or a blend of one or more polyhydric alcohols with other plasticisers is preferred, for example, a blend of glycerol with a sorbitol solution or a blend of glycerol with a sorbitol/sorbitan mixture.

The soft gelatin capsule compositions additionally include water (which is evaporated off on drying) and may additionally include other additives such as opacifiers, e.g. silicone oil, preservatives, e.g. potassium sorbate and colours.

The soft gelatin capsule shell composition (before drying) preferably comprises 30-53 parts gelatin or substituted gelatin, 15-48 parts plasticiser and 16-40 parts water, the parts being by weight of the total weight of the composition.

In the dried capsule, the gelatin or substituted gelatin usually amounts to 40-70% and the plasticiser to 10-50% by weight of the total weight of the composition.

A typical soft gelatin capsule composition (after drying) comprises essentially

Gelatin	57.65% w/w
Glycerin	28.95% w/w
Silicone Oil	13.14% w/w
Potassium Sorbate	0.26% w/w

A hard gelatin capsule shell is preferably prepared from a capsule composition comprising gelatin and a small amount of plasticiser such as glycerol.

As an alternative to gelatin, the capsule shell may be made of a carbohydrate material.

The capsule composition may additionally include colourings, flavourings and opacifiers as required.

The absorption promoter of a pharmaceutical composition present in a capsule in accordance with the invention is preferably an organic aromatic carboxylic acid or ester or amide thereof. Examples are salicylic acid and salicylates such as 5-methoxysalicylic acid; 5-methylsalicylic acid; 3-methylsalicylic acid; 5-tert-octylsalicylic acid; 3-tert-butyl-6-methylsalicylic acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-5-methyl-salicylic acid; 5-bromosalicylic acid; 3,5-diiodosalicylic acid; 3-methoxysalicylic acid; 5-octyloxysalicylic acid; 5-butoxysalicylic acid; 5-chlorosalicylic acid; and the sodium salts thereof.

Other examples are homovanillic acid; 2,5-dihydroxybenzoic acid; 2,4-dihydroxybenzoic acid; 5-methoxy-2-hydroxyphenylsulfonic acid; guaicolsulfonic acid; 2-hydroxyphenylacetic acid; 2-hydroxyphenyl-methanesulfonic acid; 5-trifluoromethyl-2-hydroxybenzoic acid; 2-hydroxy-3-methoxy-benzoic acid; and the sodium salts thereof.

Other useful absorption promoters are surface active agents such as a mixture of a) a higher fatty acid salt and b) a fatty alcohol or glyceride. The glyceride may be a mono- or di-glyceride.

A preferred surface active agent is a mixture of sodium laurate with cetyl alcohol, stearyl alcohol, glyceryl monostearate or glyceryl monocaproate, especially a sodium laurate/cetyl alcohol mixture.

The choice of absorption promot r depends upon the drug and promoters which enhance absorption of peptides or proteins such as insulin, pentagastrin and gastrin with particularly xcell nt effects are 5-methoxysalicylic acid; salicylic acid; 2,5-dihydroxybenzoic acid; 2,4-dihydroxybenzoic acid; 3-methylsalicylic acid; 5-methylsalicylic acid; 5-tert-octylsalicylic acid; 3-tert-butyl-6-methylsalicylic acid; 3,5-diisopropyl-salicylic acid; 3-tert-butyl-5-m thylsalicylic acid; 5-bromosalicylic acid; 3,5-dibromosalicylic acid; 5-

iodosalicylic acid; 3,5-diiodosalicylic acid; 2-hydroxy-phenylacetic acid; 5-trifluoromethyl-2-hydroxybenzoic acid; 3-methoxysalicylic acid; 5-octyloxysalicylic acid; 5-butoxy-salicylic acid; 5-chlorosalicylic acid; 2-hydroxy-3-methoxybenzoic acid; and the sodium salts thereof.

Good absorption of insulin is also achieved using a sodium laurate/cetyl alcohol (1:4) surfactant mixture.

Promoters which enhance the absorption of β-lactam antiobiotic drugs such as penicillin G, ampicillin, amoxicillin,methacillin, carbenicillin, cefoxitin, cephamandole, cephaprin, cephmetazole, cephanone, oxacephalosporin, and N-formimidoyl thienamycin with particularly excellent effects are 5-methoxy-salicylic acid; salicylic acid; homovanillic acid; 2,5-dihydroxybenzoic acid; 2,4-dihydroxybenzoic acid; 5-methoxy-2-hydroxyphenylsulfonic acid; 3-methylsalicylic acid; 5-methylsalicylic acid; 5-tertoctylsalicylic acid; 3-tert-butyl-6-methylsalicylic acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-5-methylsalicylic acid; guaicolsulfonic acid; 5-bromosalicylic acid; 3,5-dibromosalicylic acid; 5-iodosalicylic acid, 3,5-diiodosalicylic acid; 2-hydroxyphenylacetic acid; 2-hydroxyphenylmethanesulfonic acid; 5-trifluoromethyl-1-hydroxybenzoic acid; 3-methoxysalicylic acid; 5-octyloxysalicylic acid; 5-butoxysalicylic acid; 3,4-dihydroxyphenylacetic acid; 5-chlorosalicylic acid; 2-hydroxy-3-methoxybenzoic acid; salicyluric acid; and the sodium salts thereof.

Generally the amount of absorption promoter in our drug forms is from 1-1000 mg in each unit dose. The percentage of absorption promoter in the total combination of drug plus absorption promoter is usually 20-95% with a preferred ratio of promoter in the total combination of promoter plus drug being 30-60%. A most preferred ratio of promoter to promoter plus drug is 50%.

In addition to the drug and absorption promoter, the pharmaceutical composition usually includes a carrier such as polyethylene glycol having a molecular weight of from 400-5000, preferably from 600-4000, and more preferably a mixture of a solid polyethylene glycol having a molecular weight of, say, 4000 and a liquid polyethylene glycol having a molecular weight of, say, 600, or an oil, for example, soya bean oil, arachis oil, or an ester of a medium chain fatty acid, for example a triglyceride of fractionated coconut oil C_{8-10} fatty acids, e.g. a caprylic/capric triglyceride mixture optionally including a small amount, say 5%, linoleic acid, or a propylene glycol diester of saturated C_{8-10} fatty acids e.g. a propylene dicaprylate/dicaprate mixture.

The coating composition is preferably a mixture of acrylic copolymers, such copolymers being commercially available under the trade name "Eudragit" (TM). Eudragits are available in a variety of forms. The mixture of copolymers may also be admixed with a further film-forming component such as ethyl cellulose (available under the trade name "Ethocel") or shellac.

Typical methacrylic acid/methacrylate copolymers are:

Eudragit RS - a copolymer derived from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)-acrylic acid esters is 1:40. The mean molecular weight of the copolymer is approximately 150,000.

Eudragit S - an anionic copolymer derived from methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the esters is approximately 1:2. The mean molecular weight of the copolymer is approximately 135,000.

Eudragit L - an anionic copolymer derived from methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester groups is approximately 1:1. The mean molecular weight of the copolymer is approximately 135,000.

Various forms of Eudragit were examined for various delivery systems and amongst satisfactory systems there may be mentioned soft gelatin capsules filled with a quantity of the order of 100 mg containing 8 iu porcine insulin, 20 mg of surfactant mixture (sodium laurate: cetyl alcohol 1:4) in arachis oil. The capsules were coated with various mixtures of Eudragit RS, L and S.

The in-vitro pH dependent release rates of coated capsules were tested by scintillation counting using ^{125}I-insulin. Two dosage forms including respective coating compositions which gave best results as regards release at a pH in the 7.5 to 8.0 range (RS1 and RS2) were chosen for further studies with rats. Such capsules were administered to male rats (270 g) and insulin absorption was measured by the determination of the resulting hypoglycaemic effect. The oral administration of the two dosage forms of choice gave a significant ($p < 0.01$) hypoglycaemia when compared with controls. Duration, course and intensity of effect were different for each of the tested formulations, as will be shown in detail hereinafter. The pre-administration of a capsule containing a surfactant did not change the glycaemic profile; the post-administration prolonged the effect of RS2 from 1 to 2 hours.

Embodiments of the invention will now be described in more detail with referenc to the following Examples and accompanying drawings which are explained later in a legend.

Examples of Pharmaceutical compositions for insertion into gelatin capsules

Examples 1-3

Three formulations, based on polyethylene glycol and containing the peptide drugs insulin, calcitonin and human growth hormone respectively, for encapsulation in capsules embodying the invention are as follows.

Ingredient	Example 1 Insulin	Example 2 Calcitonin (Pork)	Example 3 Human Growth Hormone
Peptide	20 i.u. (ca.1mg)	80 i.u. (ca.1mg)	4 i.u. (ca.2mg)
Sodium 5-methoxy salicylate (1)	150.0mg	150.0mg	150.0mg
PEG 4000 (2)	3.5mg	3.5mg	3.5mg
PEG 600 (3)	187.5mg	187.5mg	186.5mg
Capsule fill wt	342 mg	342 mg	342 mg

(1) absorption promoter

(2) polyethylene glycol having a molecular weight of 4000 - a solid thickener which increases viscosity and allows suspension of solid particles.

(3) polyethylene glycol having a molecular weight of 600 - a liquid suspending agent.

The quantities of each ingredient may be varied from the above for other drugs to obtain optimum formulations and therapeutic efficacy.

The above formulations are designed to be accommodated into a hard or a soft gelatin capsule.

Where the above formulations are encapsulated within soft gelatin capsules the shell comprises

Gelatin	57.65% w/w
Glycerin	28.95% w/w
Silicone Oil	13.14% w/w
Potassium Sorbate(preservative)	0.26% w/w

Examples 4 - 6

Three oil based formulations containing the peptide drugs insulin, calcitonin and human growth hormone respectively, for encapsulation in capsules embodying the invention are as follows.

Ingredient	Example 4 Insulin	Example 5 Calcitonin (Pork)	Example 6 Human Growth Hormone
Peptide	20 i.u. (ca.1mg)	80 i.u. (ca.1mg)	4 i.u. (ca.2mg)
Sodium 5-methoxy salicylate (1)	150.0mg	150.0mg	150.0mg
Fat Mix (5)	15.0mg	15.0mg	15.0mg
Soya lecithin (2)	3.0mg	3.0mg	3.0mg
Tween(TM) 80 (3)	7.5mg	7.5mg	7.5mg
Miglyol(TM) 812(4)	123.5mg	123.5mg	122.5mg
Capsule fill wt.	300.0mg	300.0mg	300.0mg

(1) absorption promoter
(2) wetting agent
(3) a 20-mole oxyethylated sorbitan monooleate surfactant
(4) A triglyceride of a fractionated coconut oil C_{8-10} fatty acids (mainly caprylic and capric),as suspension medium
(5) thickener

The above formulations are encapsulated within hard gelatin capsules, or within soft gelatin capsules of the shell formulation given for Examples 1-3.

Examples 7-9

Three oil based formulations similar to those of Examples 4-6 but containing larger concentrations of surfactant are as follows.

Ingredient	Example 7 Insulin	Example 8 Calcitonin (Pork)	Example 9 Human Growth Hormone
Peptide	20 i.u. (ca.1mg)	80 i.u. (ca.1mg)	4 i.u. (ca.2mg)
Sodium 5-methoxy salicylate	150.0mg	150.0mg	150.0mg
Fat Mix	15.0mg	15.0mg	15.0mg
Soya lecithin	3.0mg	3.0mg	3.0mg
Tween 80	45.0mg	45.0mg	45.0mg
Miglyol 812	86.0mg	86.0mg	85.0mg
Capsule fill wt.	300.0mg	300.0mg	300.0mg

The above formulations of Examples 7 - 9 are designed to be accommodated into soft or hard gelatin capsules, for example, soft gelatin capsules of the shell formulation given in Examples 1 - 3. Formulations containing high surfactant concentrations (Examples 7-9) may promote self-emulsification of the capsule contents in an aqueous medium. Furthermore at such high concentrations, the surfactant will additionally assist in absorption promotion.

In each formulation type, the quantities of each ingredient may be varied for a given drug to obtain optimum formulations and therapeutic efficacy. The choice of a surfactant is not restricted to Tween 80; other surfactants satisfying regulatory and performance requirements may alternatively be employed.

Examples of capsules embodying the invention

The drugs and additives used for the dosage form formulations were: porcine insulin Leo Neutral 100 iu ml^{-1} (Nordisk Gentofte, Denmark) and ^{125}I porcine insulin (NEN) with a specific activity of 99μCi μg^{-1} and a radiochemical purity of 98%. Sodium laurate and cetyl alcohol (Sigma) were "chemically pure" substances and arachis oil conformed to the B.P. requirements.

Dosage Form Design :

The oral dosage form design was based on the incorporation of an insulin formulation into soft gelatin capsules coated with polyacrylic polymer - Eudragit (TM) (Rohm Pharma, Germany) - having pH-dependent solubility properties. The soft capsules were filled with various compositions according to their use during the experiment. The compositions are presented in Table 1. Organic solvent solutions of Eudragit RS, L and S at various ratios were used to coat the capsules (Table 2).

Preparation of the Formulation (Table 1)

800 μl of porcine insulin solution (Leo Neutral) was mixed with 40 mg sodium laurate and 160 mg cetyl alcohol (small pieces) and was heated to 40 • C. The arachis oil was added to obtain 1000 mg preparations. Soft gelatin capsules containing arachis oil were emptied using a syringe and filled with the active preparation. The whole was closed with melted gelatin.

In Vitro Insulin Release Measurements :

The coating effectiveness was tested in vitro using the USP disintegration apparatus USP XIX, 1975. The release media used were artificial gastric juice (60 ml N HCl per litre) and buffer phosphate solutions of respective pH's 6.0, 6.5, 7.0, 7.5 and 8.0. In each experiment six capsules were tested for 1 hour in gastric juice, briefly rinsed with distilled water and transferred to a phosphate buffer solution.

The in vitro pH-dependent release course was tested by scintillation counting using ^{125}I insulin diluted with cold insulin (Table 1), the USP dissolution basket and 400 ml phosphate buffer solution. Each value given is the mean of 3 experiments.

Animal Experimental Design :

Results obtained by direction of insulin into selected regions of the gastro-intestinal lumen suggested that it would be worthwhile to investigate the effectiveness of oral dosage forms designed to deliver insulin in the presence of an absorption promoter in that part of the intestine where the proteolysis is relatively low.

The rationale of choosing gelatin capsules as dosage forms is based on the wide formulation possibilities offered by this form: 1) incorporation of oily compositions in which insulin and promoter are molecularly dispersed, 2) coating for targeting the drug release into the colon.

Hebrew University strain male rats (270 g) were starved for 20 hours before the experiment. During the experiment the rats received water ad libitum. The capsules were administered to the rats according to the study design presented in Scheme 1. The absorption of the intact insulin was evaluated by measuring the hypoglycaemic effect. Blood was collected from the rats' tails immediately before capsule administration and at $\frac{1}{2}$, 1, 2, 3, 4 and 6 hours afterwards. The rats were ether-anaesthetized during blood collection. Blood glucose concentrations were determined at 610 nm using the GOD-Perid method (Boehringer, Germany).

The formulations presented herein were selected from a number of compositions screened for the effects of: chain length (C_{10}-C_{16}) of the anionic surfactant used as absorption promoter, composition of the mixed emulsifiers and viscosity. The capsules were coated with mixtures of various ratios of Eudragit RS, S and L (Table 2) and tested for disintegration and insulin release properties by the procedures described above. Some of the relevant release profiles are presented in Figures 1 and 2.

Figure 1 shows the time release course at pH's 7.5 and 8.0 of two formulations, RS1 and RS2, selected to be orally administered to rats. The drug percent released was estimated from the ^{125}I insulin counted by scintillation. It can be observed that the time required for 95% of the drug to be released is relatively short, 15 to 40 minutes, and depends on coating and pH. Although for both formulations the time is shorter at pH 8.0 than at pH 7.5, the rate of release from RS1 is much slower than from RS2; thus, the percent released in the first fifteen minutes was 95% versus 53% for RS2 and RS1, respectively. A lag tim of two minutes could be detected at pH 8.0; whereas at pH 7.5, the release process was instantaneous. These release

properties of RS1 and RS2 are convenient for the colon content milieu. Moreover, their choice was based on the release behaviour in a wide pH range (6 to 8) as presented in Figure 2. Th pH-dependent release courses indicate that formulations RS1 and RS2 do not release detectable amounts of insulin at a pH lower than pH 7. The other formulations tested, RS, RS3 and LS, release considerable amounts of drug at pH 6.5 and pH 7.0 corresponding to upper-intestinal regions. These formulations were considered unsuitable for our purpose even though their release rates at pH's 7.5 and 8.0 were higher than that of the chosen formulations RS1 and RS2 (Figure 2).

The selected capsules were administered to rats following the protocol presented in Scheme 1, and the results were compared with those obtained by intraperitoneal administration of 4 iu neutral insulin.

The mean of the blood glucose concentration of the samples prior to dosage administration was used as a baseline for plotting the response versus time curves. Figure 3 presents the changes in blood glucose concentration that occurred after oral and intraperitoneal treatment. It is interesting to note the lag time of two hours that occurred for each insulin oral regime tested. The effect of RS2 is higher (45% reduction in glycaemia) but shorter (it lasted for about one hour) than RS1.

It was suggested that one of the causes of the short duration of enteral administration of insulin with promoter may reside in a difference in the absorption rate, from the intestinal tract, of insulin and promoter. To test this hypothesis, capsules containing only the surfactant were administered, in one trial before and in one trial after insulin administration. No change was observed by pre-treatment. However, the surfactant given 30 minutes post-insulin oral treatment extended the duration of RS2 by about one hour, improving the drug bioavailability. Similar results have been obtained by Nishihata et al, J. Pharm, Pharmacol. (1985), 37, 22-26, who reported that post-administration of promoter (enamine) in rectal dosage of insulin in dogs improved the bioavailability from 19.4% to 38.2%.

Curves of % glucose and % glucose reduction versus time were plotted (see Figures 3 and 4) and the area under the % glucose reduction versus time curve (AUC), the maximum glucose reduction (C_{max}) and the time of the maximum effect (t_{max}) were estimated from these curves. Their values are given in Table 3. A schematic comparison of the AUC of orally administered insulin (RS2) and intraperitoneally administered insulin clearly indicates that the oral preparation is effective, but its bioavailability is relatively low. The C_{max} obtained with formulation RS2 (p 0.01) and the prolongation effect of post-adminstration of promoter are worth noting.

Table 1

Composition for soft gelatin capsules			
Materials	Caps.Ins.1*	Caps.Ins.2**	Caps Surf**
Porcine insulin	8 iu	8 iu	-
^{125}I insulin (porcine)	5 μCi	-	-
Sodium laurate	4 mg	4 mg	4 mg
Cetyl alcohol	16 mg	16 mg	16 mg
Arachis oil to	100 mg	100 mg	100 mg

* tested in vitro

**administered in vivo

Caps. Ins.1 - capsules containing labelled insulin, insulin diluent and surfactant.

Caps. Ins.2 - capsules containing insulin, diluent and surfactant.

Caps. Surf. - capsules containing no insulin but containing surfactant.

Scheme 1

No.of rats	No. of caps. administered per rat		
	Caps. Ins. (RS1)	Caps. Ins. (RS2)	Caps Surf. (RS2)
5	2	-	-
5	-	2	-
5	-	2	1*
5	-	2	1**
4	-	-	2

Given 30 minutes *after **before insulin capsules' administration.
The above insulin capsules all contain the formulation referred to as Caps.Ins.2 in Table 1, which includes surfactant.

Table 2

The Eudragit RS, S and L ratios used for coating the capsules*			
Formulation	Eudragit		
	RS	S	L
RS	2	-	8
RS1	4	6	-
RS2	2	2	6
RS3	1	-	9
LS	-	7	3

*solvents: acetone and isopropyl alcohol

Table 3

Some pharmacokinetic parameters related to the hypoglycaemic effect in rats of insulin upon oral administration of soft capsules coated with Eudragit compared with intraperitoneal administration.

Treatment		Loading dose	Dose	AUC	$\underline{C}_{max}$	$\underline{t}_{max}$
		iu	iu kg^{-1}		% glucose reduction	hr.
i .p.		4	15	258	58	2
p.o.	RS1	16	59	110	45	3
	RS2	16	59	96	32	3
	RS2 + Surf	16	59	131	42	3

i.p. intra-peritoneal
p.o. oral

Legend

Figure 1. Release profiles of insulin from capsules coated with Eudragit mixtures tested at pH 7.5 and pH 8. Formulations:
○ RS1 □ RS2

Figure 2 Effect of pH on the release rate of insulin from soft capsules coated with various mixtures of Eudragit S, L and RS (se description of Fig. 3 below).

Figure 3 Hypoglycemic effect of insulin adminstered orally to normal rats by means of coated soft capsules containing an absorption enhancing formulation (for formulations see Table 1) Symbols for Figures 2 and 3:
¤ 2 capsules RS1, ○ 2 capsules RS2,
□ 2 capsules RS2 + 1 capsule surfactant post-insulin administration,
● insulin i.p. 4 iu, ✶ 2 capsules surfactant (no insulin). Each point is the mean ± SD of 5 animals for insulin administration and of 4 animals for controls.

Figure 4. Area under the curve (AUC) of the % blood glucose reduction versus time (hr.) profile upon oral administration of 16 iu insulin in coated capsules as compared with intraperitoneal administration of 4 iu insulin.

The use of a coating, such as a Eudragit coating, especially a Eudragit RS1 or RS2 coating as described above on a gelatin capsule with a pharmaceutical composition containing an absorption promoter within the capsule provides an excellent delivery system enabling oral administration of a drug which until now could only be administered by injection.

Claims

1. A capsule for oral administration, which capsule comprises a capsule shell coated with a film of a film forming composition and containing a pharmaceutical composition,
which pharmaceutical composition comprises a systemically active ingredient susceptible to attack by digestive juices and an absorption promoter, and which film forming composition comprises an acrylic polymer, characterised in that the acrylic polymer is a mixture of acrylic copolymers such that the film is sufficiently insoluble at a pH below 7 as to be capable of protecting the capsule shell and pharmaceutical composition therein from the digestive juices until the capsule reaches the jejunum or colon for absorption of the active ingredient into the bloodstream, and absorption being enhanced by the absorption promoter.

2. A capsule according to claim 1, wherein the acrylic polymer is a mixture of two acrylic copolymers, a first said copolymer being derived from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, the molar ratio of the said quarternary ammonium groups:the said ester groups being about 1:40, and having a mean molecular weight of about 150,000, and a second said copolymer being derived from methacrylic acid and methyl methacrylate, the molar ratio of free carboxyl:ester groups being about 1:2, and having a mean molecular weight of about 135,000, the said first and second copolymers being present in the mixture in a proportional amount of 2:3 respectively.

3. A capsule according to claim 1 or claim 2, wherein the acrylic polymer is a mixture of three acrylic copolymers; a first said copolymer being derived from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, the molar ratio of the said quaternary ammonium groups:the said ester groups being about 1:40, and having a mean molecular weight of about 150,000, a second copolymer being derived from methacrylic acid and methylmethacrylate, the molar ratio of free carboxyl:ester groups being about 1:2, and having a mean molecular weight of about 135,000, and a third said copolymer being derived from methacrylic acid and methyl methacrylate, the molar ratio of free carboxyl:ester groups being about 1:1 and having a mean molecular weight of about 135,000, the said first, second and third copolymers being present in the mixture in a proportional amount of 1:1:3 respectively.

4. A capsule according to any preceding claim wherein the active ingredient is a peptide or protein.

5. A capsule according to claim 4, wherein the active ingredient is insulin.

6. A capsule according to claim 5, wherein the active ingredient is gastrin, pentagastrin, calcitonin, human growth hormone, glucagon, adrenocorticotrophic hormone, leutinising releasing hormone, enkephalin, oxycotin, parathyroid hormone, thyrotropic releasing hormone or vasopressin.

7. A capsule according to any preceding claim, wherein the absorption promoter is a surface active agent.

8. A capsule according to claim 7, wherein the surface active agent is a mixture of a) a higher fatty acid salt and b) a fatty alcohol or glyceride.

9. A capsule according to claim 8, wherein the component b) is a mono- or di-glyceride.

10. A capsule according to claim 8, wherein the higher fatty acid salt is sodium laurate and the fatty alcohol or glyceride is cetyl alcohol, stearyl alcohol, glyceryl monostearate or glyceryl monocaproate.

11. A capsule according to any one of the preceding claims, wherein the pharmaceutical composition contains a pharmaceutically acceptable carrier.

12. A capsule according to claim 11, wherein the carrier is an oil.

13. A capsule according to claim 12, wherein the oil is arachis oil.

14. A capsule according to claim 11, wherein the carrier comprises polyethylene glycol having molecular weight of from 400-4000.

15. A capsule according to any one of the preceding claims, wherein the capsule shell comprises a gelatin composition.

Patentansprüche

1. Kapsel zur oralen Verabreichung, welche Kapsel eine Kapselhülle umfaßt, die mit einem Film einer filmbildenden Zusammensetzung beschichtet ist und eine pharmazeutische Zusammensetzung enthält, welche pharmazeutische Zusammensetzung einen systemischen Wirkstoff umfaßt, der für Angriff durch Magensäfte anfällig ist, und einen Absorptionspromoter umfaßt, und welche filmbildende Zusammensetzung ein Acrylpolymer umfaßt, dadurch gekennzeichnet, daß das Acrylpolymer eine Mischung aus Acrylcopolymeren ist, sodaß der Film bei einem pH-Wert unter 7 hinreichend unlöslich ist, damit er fähig ist, die Kapselhülle und pharmazeutische Zusammensetzung darin vor den Verdauungssäften zu schützen, bis die Kapsel zur Absorption des Wirkstoffs in den Blutkreislauf den Leerdarm oder Dickdarm erreicht, wobei die Absorption durch den Absorptionspromoter verstärkt wird.

2. Kapsel nach Anspruch 1, worin das Acrylpolymer eine Mischung aus zwei Acrylcopolymeren ist, wobei ein erstes genanntes Copolymer aus Acryl- und Methacrylsäureestern mit einem geringen Gehalt an quaternären Ammoniumgruppen abgeleitet ist, wobei das Molverhältnis zwischen den genannten quaternären Ammoniumgruppen und den genannten Estergruppen etwa 1:40 beträgt, und ein mittleres Molekulargewicht von etwa 150.000 aufweist, und wobei ein zweites genanntes Copolymer aus Methacrylsäure und Methylmethacrylat abgeleitet ist, wobei das Molverhältnis zwischen freiem Carboxyl und Estergruppen etwa 1:2 beträgt, und ein mittleres Molekulargewicht von etwa 135.000 aufweist, wobei die genannten ersten und zweiten Copolymere in der Mischung in einem Mengenverhältnis von jeweils 2:3 vorhanden sind.

3. Kapsel nach Anspruch 1 oder Anspruch 2, worin das Acrylpolymer eine Mischung aus drei Acrylcopolymeren ist; wobei ein erstes genanntes Copolymer von Acryl- und Methacrylsäureestern mit einem geringen Gehalt an quaternären Ammoniumgruppen abgeleitet ist, wobei das Molverhältnis zwischen den genannten quaternären Ammoniumgruppen und den genannten Estergruppen etwa 1:40 beträgt, und ein mittleres Molekulargewicht von etwa 150.000 aufweist, wobei ein zweites Copolymer von Methacrylsäure und Methylmethacrylat abgeleitet ist, wobei das Molverhältnis zwischen freiem Carboxyl und Estergruppen etwa 1:2 ausmacht, und ein mittleres Molekulargewicht von etwa 135.000 aufweist, und wobei ein drittes genanntes Copolymer von Methacrylsäure und Methylmethacrylat abgeleitet ist, wobei das Molverhältnis zwischen freiem Carboxyl und Estergruppen etwa 1:1 ist, und ein mittleres Molekulargewicht von etwa 135.000 aufweist, wobei die genannten ersten, zweiten und dritten Copolymere in der Mischung in einem Mengenverhältnis von jeweils 1:1:3 vorhanden sind.

4. Kapsel nach einem der vorhergehenden Ansprüche, worin der Wirkstoff ein Peptid oder Protein ist.

5. Kapsel nach Anspruch 4, worin der Wirkstoff Insulin ist.

6. Kapsel nach Anspruch 5, worin der Wirkstoff Gastrin, Pentagastrin, Calcitonin, menschliches Wachstumshormon, Glucagon, adrenocorticotrophes Hormon, leutinisierendes Freisetzungshormon, Enkepha-

lin, Oxycotin, Parathyroidhormon, thyrotropes Freisetzungshormon oder Vasopressin ist.

7. Kapsel nach einem der vorhergehenden Ansprüche, worin der Absorptionspromoter ein oberflächenaktives Mittel ist.

8. Kapsel nach Anspruch 7, worin das oberflächenaktive Mittel ein Mischung aus a) einem höheren Fettsäuresalz und b) einem Fettalkohol oder Glycerid ist.

9. Kapsel nach Anspruch 8, worin der Bestandteil b) ein Mono- oder Diglycerid ist.

10. Kapsel nach Anspruch 9, worin das höhere Fettsäuresalz Natriumlaurat ist und der Fettalkohol oder das Glycerid Cetylalkohol, Stearylalkohol, Clycerylmonostearat oder Glycerylmonocaproat ist.

11. Kapsel nach einem der vorhergehenden Ansprüche, worin die pharmazeutische Zusammensetzung einen pharmazeutisch verträglichen Träger enthält.

12. Kapsel nach Anspruch 11, worin der Träger ein Öl ist.

13. Kapsel nach Anspruch 12, worin das Öl Erdnußöl ist.

14. Kapsel nach Anspruch 11, worin der Träger Polyäthylenglykol mit einem Molekulargewicht von 400-4000 umfaßt.

15. Kapsel nach einem der vorhergehenden Ansprüche, worin die Kapselhülle eine Gelatinezusammensetzung umfaßt.

Revendications

1. Capsule pour administration orale, laquelle capsule comprend une enveloppe de capsule enduite d'un film ou d'une composition filmogène et contenant une composition pharmaceutique,

laquelle composition pharmaceutique comprend un ingrédient actif sur l'organisme sensible à une attaque par les sucs digestifs et un promoteur d'absorption et laquelle composition filmogène comprend un polymère acrylique, caractérisée en ce que le polymère acrylique est un mélange de copolymères acryliques de manière que le film soit suffisamment insoluble à un pH inférieur à 7 pour être capable de protéger l'enveloppe de la capsule et la composition pharmaceutique qui s'y trouve par rapport aux sucs digestifs jusqu'à ce que la capsule atteigne le jéjunum ou le côlon pour une absorption de l'ingrédient actif dans le courant sanguin, l'absorption étant améliorée par le promoteur d'absorption.

2. Capsule selon la revendication 1, où le polymère acrylique est un mélange de deux copolymères acryliques, un premier copolymère étant dérivé des esters d'acides acrylique et méthacrylique ayant une faible teneur en groupes ammonium quaternaire, le rapport molaire des groupes ammonium quaternaire auxdits groupes esters étant d'environ 1:40, et ayant un poids moléculaire moyen d'environ 150.000, et un second copolymère étant dérivé de l'acide méthacrylique et du méthacrylate de méthyle, le rapport molaire du carboxyle libre:groupes esters étant d'environ 1:2 et ayant un poids moléculaire moyen d'environ 135.000, lesdits premier et second copolymères étant présents dans le mélange en une quantité proportionnelle de 2:3, respectivement.

3. Capsule selon la revendication 1 ou la revendication 2, où le polymère acrylique est un mélange de trois copolymères acryliques ; un premier copolymère étant dérivé des esters d'acidesacrylique et méthacrylique avec une faible teneur en groupes ammonium quaternaire, le rapport molaire desdits groupes ammonium quaternaire: lesdits groupes esters étant d'environ 1:40 et ayant un poids moléculaire moyen d'environ 150.000, un deuxième copolymère étant dérivé d'acide méthacrylique et de méthacrylate de méthyle, le rapport molaire du groupe carboxyle libre:groupe ester étant d'environ 1:2 ,et ayant un poids moléculaire moyen d'environ 135.000 et un troisième copolymère étant dérivé d'acide méthacrylique et de méthacrylate de méthyle , le rapport molaire du carboxyle libre:groupes esters étant d'environ 1:1, et ayant un poids moléculaire moyen d'environ 135.000, lesdits premier, deuxième et troisième copolymères étant présents dans le mélange en une quantité proportionnelle de

1:1:3, respectivement.

4. Capsule selon toute revendication précédente où l'ingrédient actif est un peptide ou une protéine.

5. Capsule selon la revendication 4 où l'ingrédient actif est l'insuline.

6. Capsule selon la revendication 5 où l'ingrédient actif est la gastrine, la pentagastrine, la calcitonine, l'hormone de la croissance humaine, le glucagon, l'hormone adrénocorticotrophique, l'hormone de libération de la lutéine l'encéphaline, l'oxycotine, l'hormone parathyroïde, l'hormone de libération thyrotropique ou la vasopressine.

7. Capsule selon toute revendication précédente où le promoteur d'absorption est un agent tensio-actif.

8. Capsule selon la revendication 7 où l'agent tensio-actif est un mélange de a) un sel d'acide gras supérieur et b) un alcool gras ou glycéride.

9. Capsule selon la revendication 8 où le composant b) est un mono- ou diglycéride.

10. Capsule selon la revendication 8 où le sel d'acide gras supérieur est le laurate de sodium et l'alcool gras ou glycéride est l'alcool cétylique, l'alcool stéarylique, le monostéarate de glycéryle ou le monocaproate de glycéryle.

11. Capsule selon l'une quelconque des revendications précédentes où la composition pharmaceutique contient un support acceptable en pharmacie.

12. Capsule selon la revendication 11 où le support est une huile.

13. Capsule selon la revendication 12 où l'huile est de l'huile d'arachide.

14. Capsule selon la revendication 11 où le support comprend du polyéthylène glycol ayant un poids moléculaire de 400-4.000.

15. Capsule selon l'une quelconque des revendications précédentes où l'enveloppe de la capsule comprend une composition de gélatine.

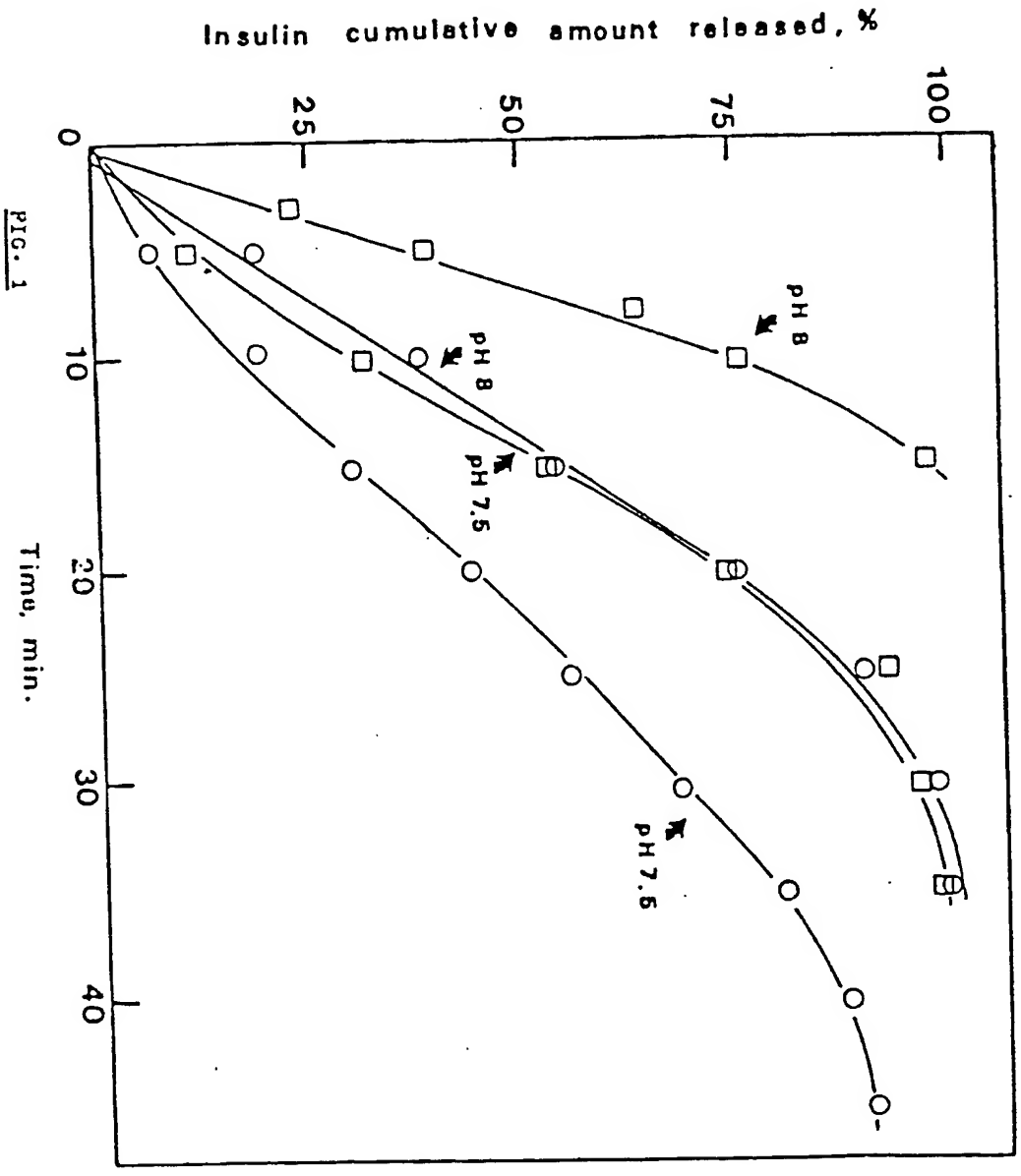
Insulin cumulative amount released, %
0
25
50
75
100
10
20
30
40
Time, min.
pH 8
pH 8
pH 7.5
pH 7.6

FIG. 1

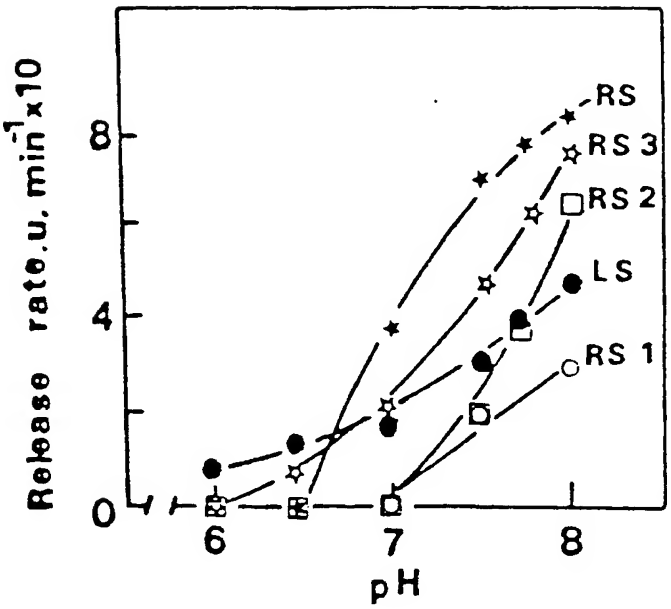

FIG. 2

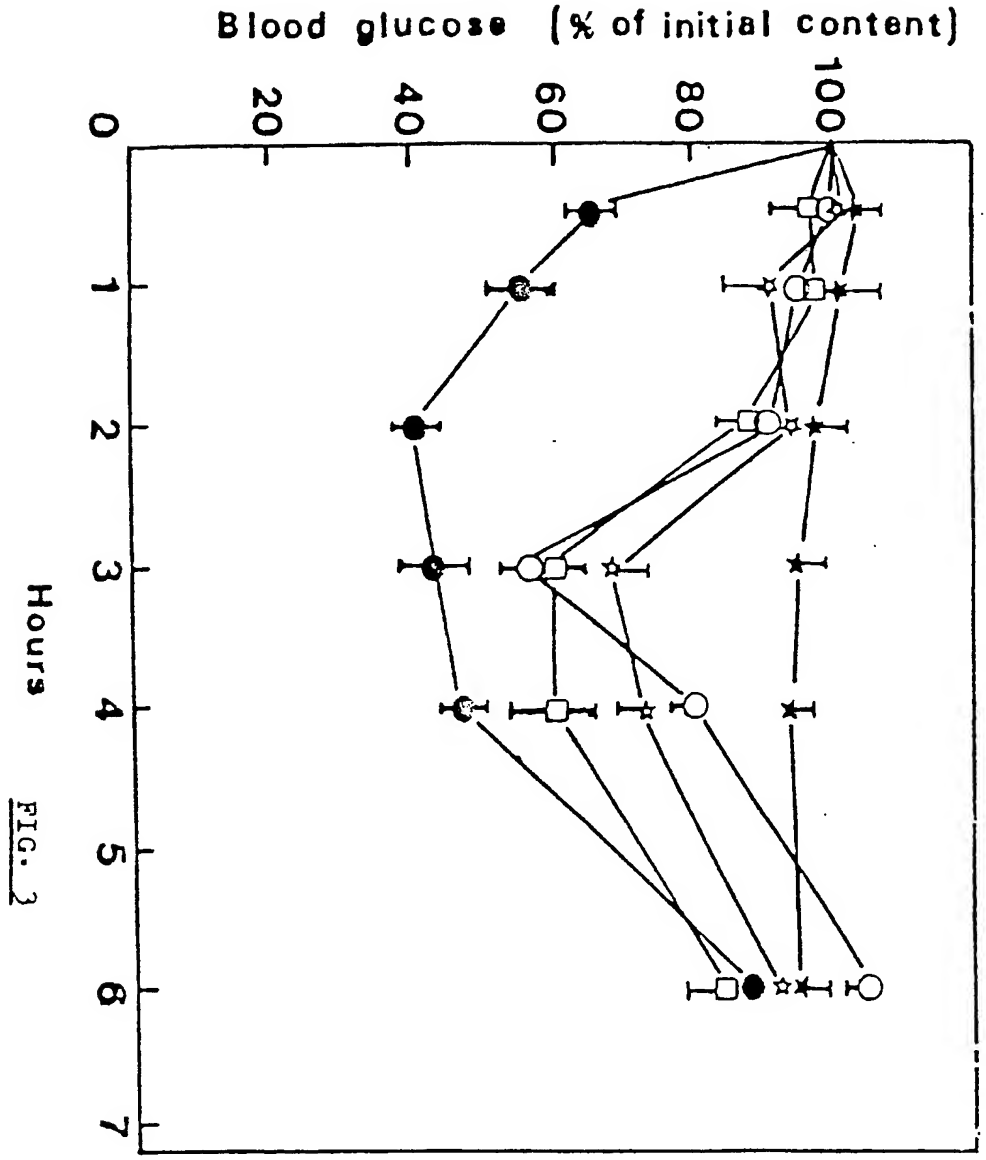
Blood glucose (% of initial content)
20
40
60
80
100
0
1
2
3
4
5
6
7
Hours

FIG. 3

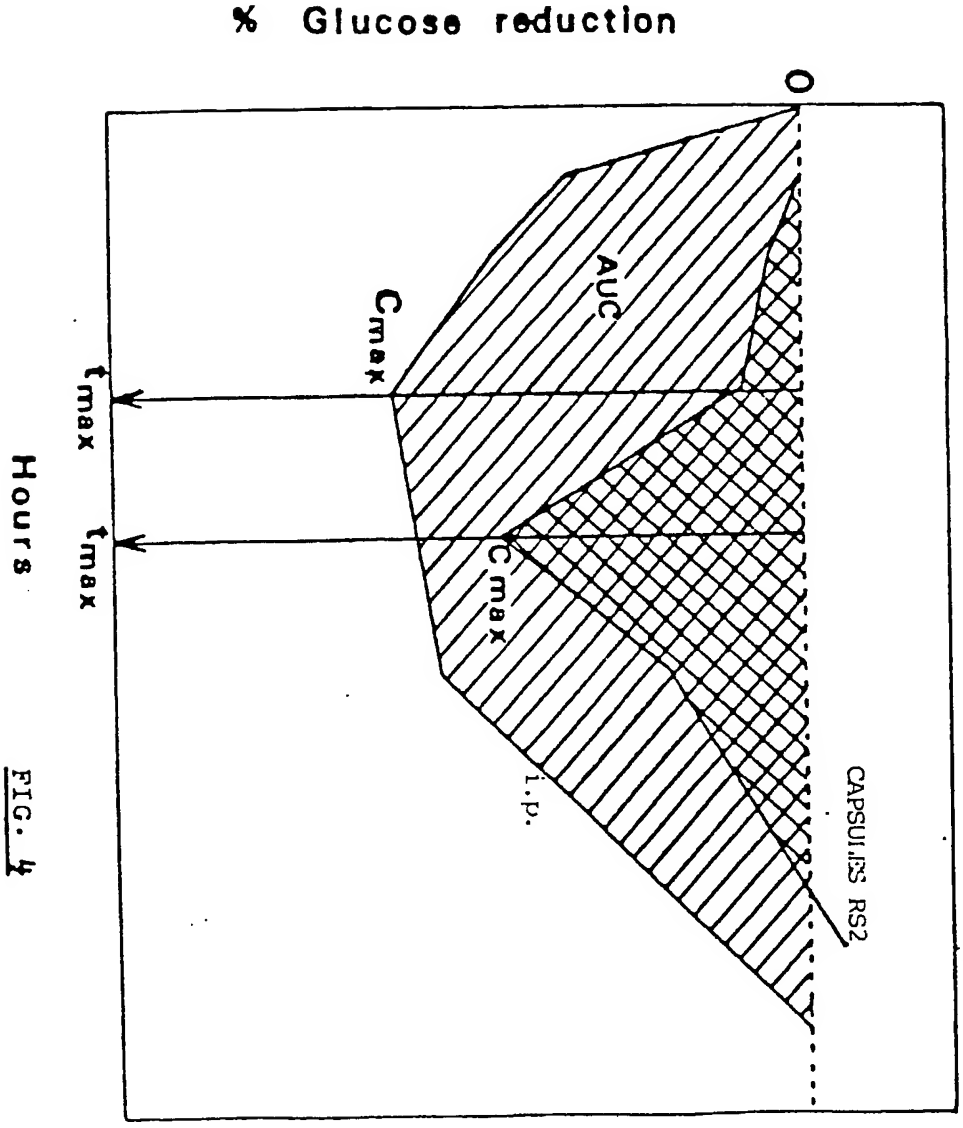
% Glucose reduction
0
AUC
C_{max}
t_{max}
t_{max}
C_{max}
i.p.
CAPSULES RS2
Hours

FIG. 4